Organocatalytic multicomponent synthesis of enantioenriched polycyclic 1,2,3,4-tetrahydro-pyridines: key substrate selection enabling regio-and stereoselectivities †

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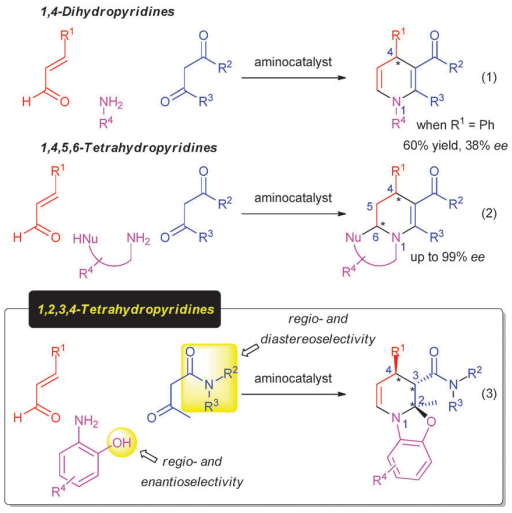
Organocatalytic multicomponent synthesis of enantioenriched polycyclic 1,2,3,4-tetrahydropyridines: key substrate selection enabling regio- and stereoselectivities†

Yohan Dudognon,‡ Haiying Du,‡ Jean Rodriguez, Xavier Bugaut* and Thierry Constantieux*

We have developed the first multicomponent synthesis of enantioenriched polycyclic 1,2,3,4-tetrahydropyridines bearing three contiguous stereogenic centers under iminium activation. The key to the success of this reaction was the use of polyfunctional substrates including 2-aminophenols and scarcely used β-ketoamides triggering a thermodynamically controlled regio- and diastereoselective sequence.

Polyhydropyridine derivatives are important structural motifs present in many natural and/or bioactive products.[1] In recent years, organocatalytic multiple bond-forming transformations (MBFTs)[2] have established themselves as a powerful method to prepare enantioenriched polyhydropyridines.[3] These syntheses generally proceed by the condensation of α,β-unsaturated carbonyl compounds either with preformed enamines,[4] or with a combination of a β-dicarbonyl and an amine.[5,6] The latter trimolecular strategy, applied either in sequential or multicomponent fashion, is synthetically more appealing as it does not require the preparation of elaborated starting materials and allow an easy decoration of the products with diverse substituents present on the three different reactants.[7,8]

The control of the sole stereogenic center found in 1,4-dihydropyridines has been achieved in 2008[5b] by a trimolecular sequential approach under iminium activation with a bulky prolinol silyl ether (Scheme 1, eqn (1)).[9] If very good results were obtained with β-alkyl enals, the enantiomeric excesses were strongly decreased with their β-aryl counterparts, because of the reversibility of the Michael addition. In the following years, several research groups implemented this reactivity pattern with functionalized amines enabling the formation of an additional bond with concomitant creation of a second stereogenic center, thereby providing 1,4,5,6-tetrahydropyridines in high yields and stereoselectivities (Scheme 1, eqn (2)).[10]

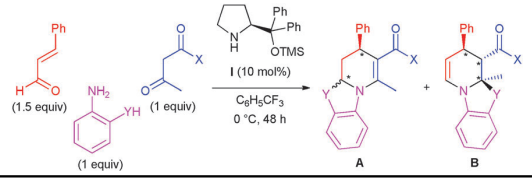


Scheme 1 Synthesis of polyhydropyridines by iminium activation.

Following our continuing interest in the development of organocatalytic enantioselective multicomponent reactions (MCRs),[10c,11] we now wish to present our recent results on the first enantioselective three-component synthesis of the regioisomeric 1,2,3,4-tetrahydropyridines[12] exhibiting a third stereogenic center, enabled by the proper choice of polyfunctional starting materials, including 2-aminophenols and β-ketoamides (Scheme 1, eqn (3)). Four new bonds and three contiguous stereogenic centers, including a tetrasubstituted one are created in this process, with complete regioselectivity and very high diastereo- and enantioselectivities.

We started our investigations by mixing *tert*-butyl acetoacetate, cinnamaldehyde and different functionalized amines in the presence of Hayashi–Jørgensen catalyst **I** in α,α,α-trifluorotoluene (Table 1). With a benzylic alcohol as the second nucleophile, only the regioisomer **A** was formed with low diastereoselectivity but good enantioselectivity (entry 1). In line with our early results on the racemic variant of this reaction,[13] we were pleased to find that the use of 2-aminophenol could partially reverse the regioselectivity,

Table 1 Selection of substrates and optimization of reaction conditions[a]

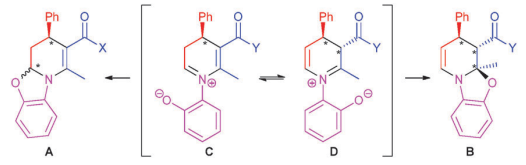


Entry	X	Y	**A**; **B** (yield[b], dr[c], ee[d])
1	O*t*-Bu	CH_2O	Only **A** (27%, 1.3 : 1 dr, 88% ee)
2	O*t*-Bu	O	**A** (12%, 1.5 : 1 dr, n.d. ee); **B** (25%, >20 : 1 dr, 94% ee)
3	O*t*-Bu	C(O)NH	No **A**; no **B**
4	N(Me)OMe	O	Only **B** (19%, >20 : 1 dr, n.d. ee)
5[e]	N(Me)OMe	O	Only **B** (28%, >20 : 1 dr, 93% ee)
6[e,f]	N(Me)OMe	O	Only **B** (32%, >20 : 1 dr, 95% ee)
7[e,g,h]	N(Me)OMe	O	Only **B** (52%, >20 : 1 dr, 95% ee)
8[e,g,i]	**N(Me)OMe**	**O**	**Only B (60%, >20 : 1 dr, 94% ee)**
9[e,g,i,j]	N(Me)OMe	O	Only **B** (50%, >20 : 1 dr, 72% ee)

[a] A solution of β-dicarbonyl (0.2 mmol, 1 equiv.), (*E*)-cinnamaldehyde (1.5 equiv.), functionalized amine (1 equiv.) and catalyst **I** (10 mol%) in $C_6H_5CF_3$ (0.10 M) was stirred at 0 °C for 48 h. [b] Isolated after silica gel column chromatography. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Determined by HPLC on a chiral stationary phase. [e] CH_2Cl_2 instead of $C_6H_5CF_3$ as the solvent. [f] BzOH (20 mol%), 24 h. [g] **I** (20 mol%), BzOH (40 mol%). [h] 96 h. [i] 10 °C, 60 h. [j] Sequential reaction: 2-aminophenol was added after two days of reaction.

affording regioisomer **B** with high stereoselectivities (entry 2), whereas anthranilamide was not a suitable substrate in MCR conditions (entry 3).

We have recently developed an organocatalytic Michael addition of β-ketoamides to nitroolefins, where the reduced acidity of the β-ketoamides compared to β-ketoesters allowed to control the diastereoselectivity of the process.[14] Analyzing our present results, we hypothesized that products **A** and **B** can arise from intermediate iminium ions **C** and **D** (Scheme 2), respectively, and that reducing the acidity of the α position could shift the equilibrium towards **D**, favoring the formation of product **B**. Indeed, when *tert*-butyl acetoacetate was replaced by the corresponding Weinreb amide, only the regioisomer **B** was formed, with very high diastereoselectivity (Table 1, entry 4). From this encouraging result, we undertook a systematic optimization of the reaction conditions,[15] during which only the expected regioisomer **B** was obtained with uniformly high enantio- and diastereoselectivity, through a cooperative kinetic and thermodynamic control from the catalyst and the substrate, respectively. The absolute configuration of the product can tentatively be attributed according to literature precedents,[5b,15] while the relative configuration was determined by 2D ^{1}H NMR studies.[15] Switching the solvent to CH_2Cl_2 was slightly beneficial for the conversion and the product was formed with 93% ee (entry 5).



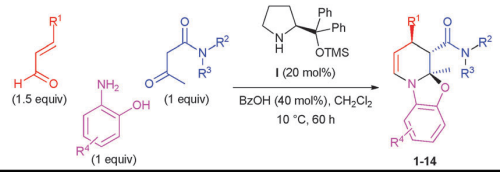
Scheme 2 Rationale for the control of the MCR's regioselectivity.

Three modifications of the reaction conditions could gradually improve the yield of product to 60%:[16] (i) adding BzOH as a co-catalyst (entry 6); (ii) increasing the catalyst loading to 20 mol% and extending the reaction time (entry 7); (iii) carrying out the reaction at 10 °C (entry 8). An attempt of sequential reaction, with addition of 2-aminophenol after two days of reaction, resulted in a decrease of the enantiomeric excess, illustrating the power of MCRs at trapping sensitive intermediates before their degradation or racemization (entry 9).

With these optimized conditions in hand, a study of the reaction scope with respect to the three reaction partners was undertaken (Table 2). In all cases, the products were isolated in moderate yields, which should however be evaluated in view of the complexity of the MCR that installs four new bonds, but with complete regioselectivities and very high diastereoselectivities. If product **2** obtained from an enal bearing an electron-donating group in *para* position was obtained with slightly reduced enantiomeric excess, electron-neutral and -poor enals afforded products **1,3–5** with good enantioselectivities. *meta*-Substitution was also well tolerated, as shown for product **6**, but, in the case of *ortho*-substituted cinnamaldehydes or aliphatic enals, the reaction was sluggish, with only small amounts of product identified by ^{1}H NMR in the crude reaction mixtures.

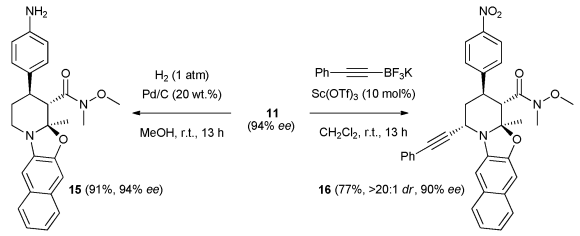
Contrary to the strong influence of the substitution of the enal, the reaction outcome did not seem to depend on the nature of the substituents on the 2-aminophenol reaction partner, as product **7–10** were obtained with similar results. With 3-amino-2-naphthol, the enantiomeric excess of product **11** culminated

Table 2 Scope of the multicomponent synthesis of 1,2,3,4-tetrahydropyridines[a]



Products	R^1	R^2, R^3	R^4	Yield[b] (%)	ee[c] (%)
1	Ph	Me, OMe	H	60	94
2	4-MeOC_6H_4	Me, OMe	H	41	82
3	4-FC_6H_4	Me, OMe	H	45	86
4	4-ClC_6H_4	Me, OMe	H	48	90
5	4-$NO_2C_6H_4$	Me, OMe	H	50	94
6	3-ClC_6H_4	Me, OMe	H	49	94
7	4-$NO_2C_6H_4$	Me, OMe	4-Cl	43	90
8	4-$NO_2C_6H_4$	Me, OMe	5-Cl	41	92
9	4-$NO_2C_6H_4$	Me, OMe	3-Me	45	90
10	4-$NO_2C_6H_4$	Me, OMe	5-Me	45	92
11	4-$NO_2C_6H_4$	Me, OMe	4,5-$(CH)_4$	55	96
11[d]	4-$NO_2C_6H_4$	Me, OMe	4,5-$(CH)_4$	53	94
12[d]	Ph	Me, OMe	4,5-$(CH)_4$	43	94
13	4-$NO_2C_6H_4$	Me, Me	H	29	92
14	4-$NO_2C_6H_4$	Bn, Bn	H	34	92

[a] A solution of β-ketoamide (0.2 mmol, 1 equiv.), enal (1.5 equiv.), aminophenol (1 equiv.), catalyst **I** (20 mol%) and BzOH (40 mol%) in CH_2Cl_2 (0.10 M) was stirred at 10 °C for 60 h. [b] Isolated after silica gel column chromatography. For all products, dr, determined by ^{1}H NMR of the crude reaction mixture, was >20 : 1. [c] Determined by HPLC on a chiral stationary phase. [d] Reaction performed on 2 mmol scale.



Scheme 3 Post-functionalization of the 1,2,3,4-tetrahydropyridines.

to 96%. Noteworthy enough, the reaction could be scaled-up to 2 mmol for products **11** and **12**, with virtually unchanged results. Not surprisingly, when using less activated tertiary amide, a decrease of the yield was observed, but products **13** and **14** were still obtained with very good selectivities.

To finish, we investigated the potential of product **1–14** for post-functionalization to obtain more structurally diverse scaffolds (Scheme 3). Starting from product **11**, catalytic hydrogenation of the enamine, accompanied by the reduction of the nitro group, delivered piperidine **15** in high yield and preserved optical purity. Moreover, treating **11** with a potassium alkynyltrifluoroborate in the presence of a catalytic amount of $Sc(OTf)_3$ installs a fourth stereogenic center, leading to **16** as a single diastereomer and only a minor erosion of enantiomeric excess.[17]

We have designed the first route towards 1,2,3,4-tetrahydropyridines based on an enantioselective MCR. Although yields of products remained moderate, they were prepared with good enantioselectivities, kinetically fixed by the catalyst, as well as complete regioselectivities and high diastereoselectivities, under thermodynamic substrate control. Our current efforts aim to develop other enantioselective MCRs for the synthesis of original chiral polycyclic architectures.

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